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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER
FALK, ANNE MARIE

ART UNIT	PAPER NUMBER
1632	

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

File

Office Action Summary	Application No.	Applicant(s)	
	09/693,043	BJORKLUND, ANDERS	
	Examiner	Art Unit	
	Anne-Marie Falk, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4, 6, 13, and 14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 13, and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *8* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The amendment filed January 16, 2003 (Paper No. 16) has been entered. Claims 1-4 and 6 have been amended. Claims 5 and 7-12 have been cancelled. Claims 13 and 14 have been newly added.

Accordingly, Claims 1-4, 6, 13, and 14 are pending in the instant application.

The following rejections are reiterated or newly applied and constitute the complete set of rejections being applied to the instant application. Rejections and objections not reiterated from the previous office action are hereby withdrawn.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6, 13, and 14 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method for transplantation of at least about 500,000 mitogenic growth factor-responsive neural stem cells capable of differentiating into neurons, oligodendrocytes, or astrocytes to the brain, wherein the cells (a) are transplanted to a first locus of the brain of a living host subject; (b) migrate in vivo after implantation from the first locus to other anatomic sites for integration within the nervous system of the host subject following infusion of a mitogenic growth factor that does not induce differentiation of the neural stem cells at a second locus of the brain of said host subject; (c) integrate *in situ* after implantation into the parenchymal tissues at a local anatomic site in the host subject; and (d) differentiate in situ after integration into a cell selected from the group consisting of neurons, oligodendrocytes, and astrocytes, wherein the transplanted neural stem cells retain their *in vivo*

responsiveness to the mitogenic growth factor. In a preferred embodiment, the neural stem cells comprise mammalian embryonic progenitor cells.

The specification fails to provide an enabling disclosure for the methods of transplantation because the specification teaches that the only use for the method is to provide a therapeutic benefit to a subject and the specification does not teach how to use the claimed methods to produce a therapeutic effect. The specification does not provide specific guidance as to how this method could be used therapeutically for any disorder. No working examples demonstrate a therapeutic effect in a diseased animal for the claimed methods. The specification contemplates that the claimed method of transplantation can be used to treat various neurodegenerative diseases and other pathological conditions (p. 16, line 29 to p. 17, line 30), such as epilepsy, stroke, ischemia, Huntington's disease, Parkinson's disease, and Alzheimer's disease (p. 16, line 30 to p. 17, line 1). The specification further contemplates use of the method of transplantation to treat demyelinating and dysmyelinating disorders, such as Pelizaeus-Merzbacher disease, multiple sclerosis, various leukodystrophies, post-traumatic demyelination, and cerebrovascular accidents, as well as various neuritis and neuropathies, particularly of the eye (p. 17, lines 20-23). Accordingly, the specification must teach how to use the claimed method of transplantation to produce a therapeutic effect. However, the specification does not teach how to produce a therapeutic effect in any animal. The specification fails to provide specific guidance relating to the site of injection and extent of cellular persistence required to provide any therapeutic benefit for any disorder. The claims are not enabled because the transplantation of neural stem cells (NSCs), including embryonic neural stem cells, into a host has not been demonstrated to provide any therapeutic benefit to the host. The specification clearly teaches that the use for the transplant methods is to produce a therapeutic effect in the host.

The specification fails to provide an enabling disclosure for the method of cell-based therapy because methods of transplantation of neural tissue are not routinely successful and the specification does not offer adequate guidance to enable one skilled in the art to practice the claimed invention to derive a

therapeutic benefit in a diseased animal. The specification teaches that the only use for the claimed method of transplantation is to produce a therapeutic effect, but the specification does not adequately teach how to use the claimed method to produce such an effect. Jackowski et al. (1995) details the limitations and unpredictability associated with the transplantation of neural tissue. At page 311, column 1, paragraph 2, the reference discusses barriers to successful transplantation of neural tissue, notably the presence of molecules that actively inhibit the regeneration of mammalian CNS and PNS axons. The specification does not teach how to overcome such problems. The specification does not offer adequate guidance as to how the claimed method could be used therapeutically for the treatment of the wide variety of disorders discussed in the specification. With regard to therapy, the specification provides general teachings only, but does not provide specific guidance for using the claimed method to treat pathological conditions. As discussed below, methods of neural stem cell transplantation are in their infancy. Therefore, considerable guidance is needed. The specification fails to provide specific guidance relating to the site of injection and the extent of cellular persistence required and attainable in practice, to provide a therapeutic benefit for the treatment of any pathological disorder.

Milward et al. (1997) demonstrates that transplantation of neural stem cells to the CNS does not produce a therapeutic effect in a diseased animal. Milward et al. describes the transplantation of canine CNS NSCs into both rat and a shaking pup myelin mutant dog. In the rat, this resulted in the production of myelin by graft-derived cells. The authors report that the grafted cells integrated normally into the adult shaking pup cytoarchitecture. Yet despite all this, the clinical deficit of these animals was not ameliorated. Thus, it is clear that the production of myelin *in vivo* and normal integration of cells is not predictive of a therapeutic outcome. Given the unpredictability in the art of therapeutic transplantation, the development of specific therapeutic protocols requires substantial experimentation.

Mehler et al. (1999) disclose that many studies have suggested that the normal adult brain may lack the appropriate environmental signals to allow neural progenitors to realize their broad lineage potential. Specific neuropathologic conditions may alter the normal balance of regional environmental

signals, for example by releasing proinflammatory and other modulatory cytokines. The presence of these inappropriate cellular cues may predispose residual neural populations to undergo apoptosis. The authors state that "[t]his suggests that it may be necessary to promote lineage commitment of progenitor cells *in vitro* prior to transplantation into a damaged brain" (p. 782, column 1, paragraph 1).

Zhang et al. (1999) report producing "robust myelination" in myelin-deficient rats upon transplantation of neural stem cells. However, despite this "robust myelination" the experiment in fact did **not** produce a therapeutic effect in the host.

Akiyama et al. (2001) describes the transplantation of clonal neural precursor cells. The cells were differentiated *in vitro* prior to transplantation. The abstract summarizes the protocol as follows:

> Neurospheres were established and the nestin-positive cells were clonally expanded in EGF and bFGF. Upon mitogen withdrawal *in vitro*, the cells differentiated into neuron- and glia-like cells as distinguished by antigenic profiles; the majority of cells in culture showed neuronal and astrocytic properties of oligodendrocytes and Schwann cells. When transplanted into the demyelinated adult rat spinal cord immediately upon mitogen withdrawal, the cells elicited extensive remyelination with a peripheral myelin pattern similar to Schwann cell myelination characterized by large cytoplasmic and nuclear regions, a basement membrane, and P0 immunoreactivity. The remyelinated axons conducted impulses at near normal conduction velocities.

The animal model used for the transplantation experiments was one in which a demyelinating lesion was induced. Applicant argues that the transplanted human neurospheres produced extensive remyelination and that the remyelinated axons conducted impulses at near normal conduction velocities. However, the method of Akiyama et al. is not supported in the specification, because the method taught by Akiyama et al. involved pre-differentiation of cloned cells in culture for 10 days prior to transplantation to generate a culture comprising Schwann-like cells. However, the instant specification teaches that neural stem cells are to be injected into a target area. Thus, the experiments of Akiyama et al. were not performed in accordance with the teachings of the specification. Moreover, the instant specification does not teach how to produce the Schwann-like cells that the Akiyama reference reports using in their transplantation

protocol. At pages 36-37 of Akiyama et al., the authors address the question of why neural precursor cells derived from adult brain differentiate into Schwann-like cells in CNS *in vivo*. The nature of the lesion and the cellular and extracellular milieu of the transplant zone are likely to substantially influence the outcome of any given protocol. The authors note that EGF-responsive neural stem cells derived from fetal rodents formed an oligodendrocyte pattern of remyelination in myelin-deficient rats. The authors suggest that this may result from differences in fetal and adult sources of the cells or a species difference. They further suggest that the myelin-deficient rat, which has an abundance of astrocytes around the amyelinated axons, could provide a trophic influence for the differentiation of oligodendrocytes. Thus, the art teaches that the results of transplantation are unpredictable and there are no clear guidelines regarding which protocols will work or which lesions can be treated with a given protocol.

The court has recognized that physiological activity is unpredictable. *In re Fisher*, 166 USPQ 18 (CCPA 1970). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved. *In re Fisher*, 166 USPQ 18 (CCPA 1970).

It is not to be left up to the skilled artisan to figure out how to make the necessary starting materials and then to figure out how to use them to produce the biological effects as recited in the claims. The courts held that the disclosure of an application shall inform those skilled in the art how to use applicant's claimed invention, not how to **find out** how to use it for themselves. *In re Gardner et al.* 166 USPQ 138 (CCPA 1970). This specification only teaches what is intended to be done and how it is intended to work, but does not actually teach how to do that which is intended.

At pages 3-5 of the response, Applicant argues that the rejection is improper because Applicant contends that when the therapeutic efficacy or benefit is questioned, the rejection is properly the subject of a 101 utility rejection on the basis that the claimed invention lacks credible utility. Applicant points to the MPEP at §§ 706.03(a)(1) and 2107. However, in the instant case the utility requirement is satisfied as the Examiner considers the asserted utility to be a credible utility, albeit one that is not enabled by the

instant specification. The MPEP states that "[i]n some instances, the use will be provided, but the skilled artisan will not know how to effect that use. In such a case, no rejection will be made under 35 U.S.C. 101, but a rejection will be made under 35 U.S.C. 112, first paragraph." See MPEP § 2164.07(II). In the instant case, for the reasons discussed herein, the use is provided (i.e., therapy), but the skilled artisan would not know how to effect that use.

Applicant asserts that numerous publications reflect the view of those skilled in the art that the claimed methods would provide a therapeutic benefit to the host.

Applicant points to Qu et al. (2001) for reporting that when human neural stem cells were transplanted into aged rats, the cells differentiated into neurons and astrocytes, that both neurons and astrocytes migrated into the cortex and hippocampus in a well-defined and organized pattern, and that the rats demonstrated significantly improved cognitive function. However, the instant specification does not provide all of the steps, or the specific conditions under which transplantation can be performed to produce neurons, oligodendrocytes, or astrocytes which then function to produce a therapeutic effect.

Applicant argues that Milward et al. (1997) show that canine CNS NSCs transplanted into both a shaking (*sh*) pup myelin mutant dog and into the myelin-deficient (*md*) rat spinal cord resulted in the production of myelin by graft-derived cells. However, as discussed above, the formation of myelin did not result in producing a therapeutic effect in the animal. Thus, Milward et al. does not demonstrate application of the claimed method to produce a therapeutic effect. Furthermore, Milward et al. demonstrate that production of myelin *in vivo* and normal integration of cells is not predictive of a therapeutic outcome.

Applicant states that Zhang et al. (1999) report producing "robust myelination" in myelin-deficient rats upon transplantation of neural stem cells. However, as discussed above, this "robust myelination" in fact did **not** produce a therapeutic effect in the host.

Applicant points to Brustle et al. (1998) for describing the implantation of fetal human CNS progenitor cells into mice that "acquire an oligodendroglial phenotype and participate in the myelination

of host axons." However, these experiments were carried out in healthy animals. Thus, no therapeutic effect was demonstrated. The function of the cells upon transplantation is not sufficient to support enablement because there is not sufficient guidance for using the transplantation method therapeutically in diseased animals, as the art demonstrates that production of myelin in vivo does not correlate with a therapeutic outcome (see Milward et al., 1997).

Applicant states that Yandava et al. (1999) show that transplantation of CNS NSCs resulted in "global" cell replacement and therapeutically effective remyelination in the dysmyelinated shiverer (*shi*) mouse brain with repletion of myelin basic protein and, in some cases, a decrease in symptomatic tremor. While some therapeutic effect was seen, in so far as a number of recipient animals showed a decline in symptomatic tremor, the method of transplantation used a cloned cell line from neonatal mouse cerebellum (p. 7030, column 1, paragraph 3). This clone was not derived in the same manner as is taught in the specification for isolating neural stem cells. Thus, as the reference does not use the neural stem cells as recited in the claims, it does not support enablement for the claimed method.

Applicant points out that Flax et al. (1998) show that human CNS NSCs transplanted into newborn meander tail (*mea*) mouse cerebella provided "replacement neurons" with the "definitive size, morphology, and location of cerebellar granule neurons." However, there is no teaching of a reduction in clinical deficit and the specification does not offer specific guidance for using this property (i.e., development of replacement neurons) to produce a therapeutic effect using the claimed method of transplantation. Sufficient reasoning has been provided to doubt that the method taught could be used without additional manipulations or without identifying special conditions under which the method could be used therapeutically. The instant specification does not provide all of the steps, or the specific conditions under which transplantation can be performed to produce neurons, oligodendrocytes, or astrocytes which then function to produce a therapeutic effect. In the absence of teachings sufficient to allow the skilled artisan to produce a therapeutic effect using the claimed method, one skilled in the art would not know how to use the claimed method.

Applicant points out that Fricker et al. (1999) show that when CNS NSCs were transplanted into neurogenic regions in the adult rat brain, the *in vitro* propagated cells migrated specifically along the routes normally taken by endogenous neuronal precursors, exhibited, substantial migration within the non-neurogenic region, and showed site-specific differentiation into both neuronal and glial phenotypes. However, the specification does not offer specific guidance for using these properties to produce a therapeutic effect using the claimed method of transplantation.

As the post-filing art demonstrates that many groups investigated a variety of protocols in a variety of experimental models with the hope of developing a therapeutic method, when the art is viewed as a whole it is evident that substantial experimentation was required to produce the limited successes achieved.

In view of the quantity of experimentation necessary to determine appropriate parameters for practicing the claimed method to achieve a therapeutic outcome, and given the lack of applicable working examples directed to therapeutic transplantation, the limited guidance provided in the specification directed to achieving migration of cells transplanted into the brain, the lack of specific guidance directed to the wide variety of disorders said to be amenable to treatment using the claimed method, the broad scope of the claims, and the unpredictability for producing a therapeutic effect upon transplantation of neural stem cells, undue experimentation would have been required by one skilled in the art to practice the claimed method of transplantation to produce a therapeutic effect.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 is indefinite in its recitation "wherein said neural stem cells comprise mammalian embryonic progenitor cells." A broad limitation together with a narrow limitation that falls within the

broad limitation (in the same claim) is considered indefinite, since the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. Note the explanation given by the Board of Patent Appeals and Interferences in *Ex parte Wu*, 10 USPQ2d 2031, 2033 (Bd. Pat. App. & Inter. 1989), as to where broad language is followed by "such as" and then narrow language. The Board stated that this can render a claim indefinite by raising a question or doubt as to whether the feature introduced by such language is (a) merely exemplary of the remainder of the claim, and therefore not required, or (b) a required feature of the claims. Note also, for example, the decisions of *Ex parte Steigewald*, 131 USPQ 74 (Bd. App. 1961); *Ex parte Hall*, 83 USPQ 38 (Bd. App. 1948); and *Ex parte Hasche*, 86 USPQ 481 (Bd. App. 1949). In the present instance, Claim 2 recites the broad recitation "progenitor cells", and the narrow recitation "neural stem cells."

Furthermore, with regard to Claim 2, cells cannot **comprise** other cells.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne-Marie Falk whose telephone number is (703) 306-9155. The examiner can normally be reached Monday through Thursday and alternate Fridays from 10:00 AM to 7:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds, can be reached on (703) 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the patent analyst, William Phillips, whose telephone number is (703) 305-3482.

Anne-Marie Falk, Ph.D.

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER